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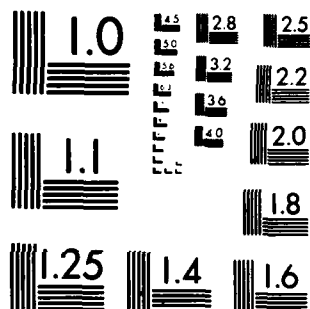
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Report Number 7

RESPONSE OF COMBINED ELECTRICAL STIMULATION AND  
BIODEGRADABLE CERAMICS

Final Report

J. E. Lemons, Principal Investigator

June, 1982

Supported by  
U.S. ARMY MEDICAL RESEARCH AND DEVELOPMENT COMMAND  
Fort Detrick, Frederick, Maryland 21701

Contract Number DAMD17-75-C-5044

University of Alabama in Birmingham  
Birmingham, Alabama 35294

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20. ABSTRACT (Continue on reverse side if necessary and identify by block number) Investigations were conducted on porous tricalcium phosphate ceramic proposed for bone replacement. Rod and granular forms were studied using the ceramic alone and in combination with autogeneous bone. Animal models included mid-shaft replacements of rabbit tibiae and dog radii. The bone lesions included the initial placement of ceramic at the first surgical procedure and at nonunion sites. In general, the biomaterial analyses showed reproducible materials with porosity that permitted bone ingrowth; minimal		

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difficulties in handling the material; bone ingrowth into the rod forms with biomechanical strengths similar to controls; variability in the rate of resorption for the rod form ceramic; minimal influence of electrical stimulation on the rate of ceramic resorption and bone ingrowth; a low probability for the correction of nonunions with the rod or granular form ceramic when used alone; a high probability of nonunion corrections when the ceramic was used with autogeneous bone; a dependence upon the relative ratio and quantity of granular form ceramic and autogeneous bone mixtures; no significant differences between -40+100 mesh or 1, 2 or 3 mm size granular materials; residual ceramic retained in dog radii implant sites at 4 years; and very acceptable tissue responses to the TCP material throughout this 1975 to 1981 study.

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## SUMMARY

This report summarizes the investigations on rod and granular form tricalcium phosphate ceramic (TCP) conducted from 1975 to 1981. The laboratory studies characterized the material while the laboratory animal studies compared mid-shaft replacements of rabbit tibiae and dog radii utilizing combinations of TCP and autogeneous bone for early and nonunion lesions.

The materials could be handled, the animal models were quite adequate and the studies showed possible applications for human surgery along with limitations. These studies have been presented in annual reports 1 through 5. This report provides a summary of salient conclusions. The reader is referred to the annual reports for detailed information.

# TABLE OF CONTENTS

<u>Summary</u> .....	Page
<u>Foreward</u> .....	2
<u>Introduction</u> .....	3
Background	
Materials and Methods	
Animal Models and Surgery	5
Animal Follow-up	
Necropsy and Histology	
<u>Results and Discussion</u> .....	9
Materials	
Surgery and Animal Follow-up	
Necropsy and Tissue Evaluations	
<u>Conclusions</u> .....	11
<u>References</u> .....	14

## FIGURES

- Figure 1. Schematic drawing of segmental lesion in a rabbit tibia showing the relative placement positions of the stabilization pins..... 7
- Figure 2. Schematic drawing of the segmental bone replacement and bone stabilization plate for the dog studies... 8



## INTRODUCTION

Synthetic substances for the replacement of autogeneous bone graft in surgery have been proposed and investigated since the earliest bone surgical procedures. Certainly, treatment modalities for maxillofacial and orthopaedic surgery have significantly changed; however, no completely acceptable synthetic material has been developed. This is especially true with respect to the treatment of segmental defects and nonunions. In general, long-term rehabilitative courses are required for such defects. It is the objective of this research, to more fully investigate a quite promising candidate synthetic bone substitute material, porous tricalcium phosphate ceramic, in order to improve conditions for surgical corrections of lesions in bone. A result of this research could be a reduction in time of treatment for maxillofacial and orthopaedic procedures, a reduction in deformities, and a reduction in morbidity.

The technical objectives of this project were as follows:

1. To develop an animal model for the study of the combined techniques of applying direct current electrical stimulation to tissue ingrowth and stabilization of porous biodegradable tricalcium phosphate ceramic.
2. To evaluate the kinetics and tissue response to biodegradable tricalcium phosphate ceramics at surgical lesions in the animal system.
3. To evaluate the kinetics and tissue response of combined electrical stimulation and porous tricalcium phosphate ceramic with the same animal system.
4. To evaluate surgical methods and combinations of the granular tricalcium phosphate ceramic and autogeneous bone for the correction of surgical lesions and nonunions in rabbits.
5. To evaluate long-term tissue responses to porous rod form tricalcium phosphate ceramic segmental replacements in dogs.
6. To compare granular forms of porous tricalcium phosphate ceramic, with average particulate dimensions of 1, 2 and 3 millimeters, for use as a mixture with 50 weight percent autogeneous bone in the rabbit animal model.

## Background

The information available in the published literature clearly demonstrates the extensive interest that has been associated with the tricalcium phosphate ceramics (TCP) over this past ten years.<sup>1-30</sup> In most all reports, the TCP has demonstrated good biocompatibility, which has resulted in these types of compounds being introduced for specific clinical situations. Future applications of this substance appear quite promising and selected applications in maxillofacial and orthopaedic surgery may initiate in the very near future.

The literature and background information on TCP has been summarized in Reports 1 to 5 on this project DAMD17-75-C-5044 and the reader is referred to these reports for more complete discussions. The presentations, abstracts and publications that have been submitted from this project are listed in the references sections.<sup>31-43</sup>

## Materials and Methods

The porous tricalcium phosphate ceramics were obtained from a single source\* for the major parts of this investigation. One group of specimens were fabricated from another TCP material\*\* early in the program, however these investigations were very limited. The samples were received as 1 X 10 cm rods from which the various rod and granular forms were fabricated. The rods were either 8 X 8 mm or 10 X 10 mm ovals. The granular forms were -40+100 mesh or 1, 2 and 3 mm sizes. All samples were dry heat sterilized. The materials were characterized by SEM and optical microscopy, by X-ray diffractions and by quantitative microscopy. These data were summarized in Reports Number 1 and 2.

## Animal Models and Surgery

The animal models utilized for these studies were the New Zealand White Rabbit and the Mongrel dog. The central portion of the rabbit tibia was an prepared surgically to evaluate the rod and granular forms of the TCP. Either 8 or 12 mm length lesion was introduced to study the kinetics of tissue infiltration into the porous rod forms, the rate of healing for granular forms with or without autogeneous bone, or the correction of nonunions. The mid-portion of the dog radius was used to investigate the long-term fate (5 years) of the rod form TCP.

The animal model bone lesion sites are shown schematically in Figures 1 and 2 for the rabbit and dog respectively.

\* Ceramic Materials Section, Battelle Memorial Institute, Columbus, Ohio  
(L. McCoy or G. Messing)

\*\*MITER, INC., Worthington, Ohio (T. Driskell)

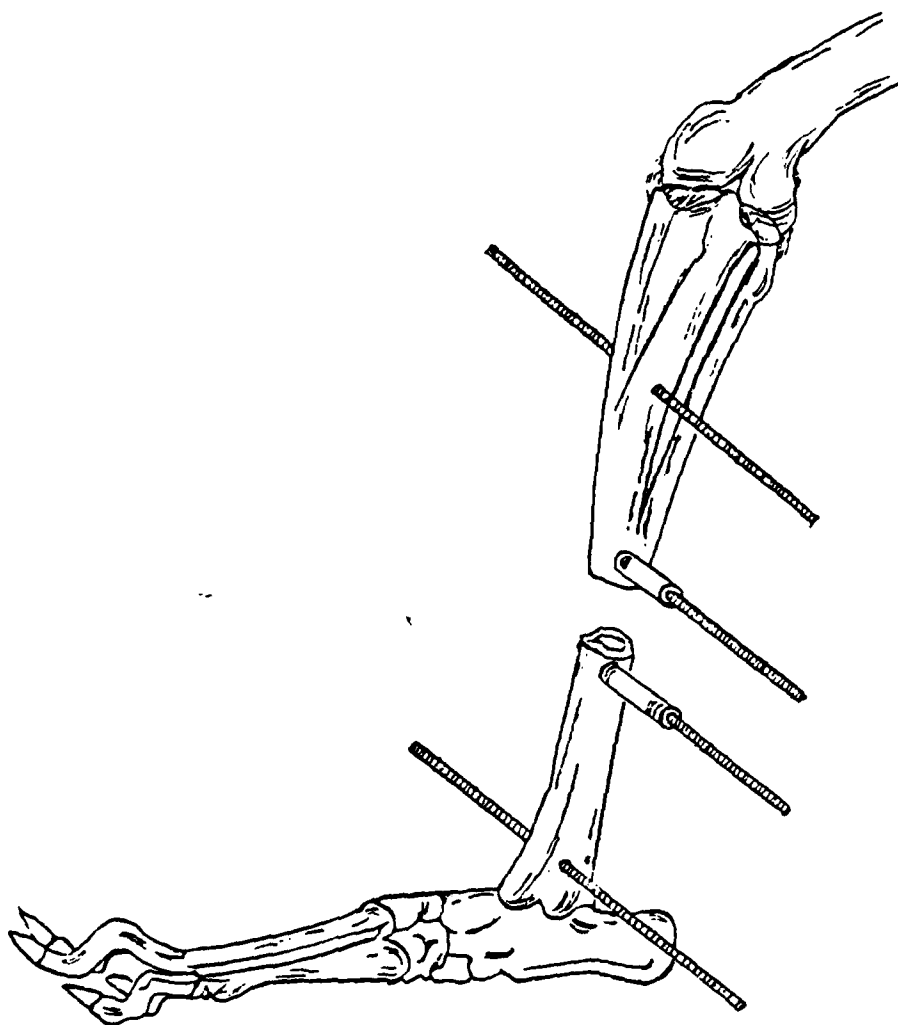


Figure 1. Schematic drawing of segmental lesion in a rabbit tibia showing the relative placement positions of the stabilization pins.

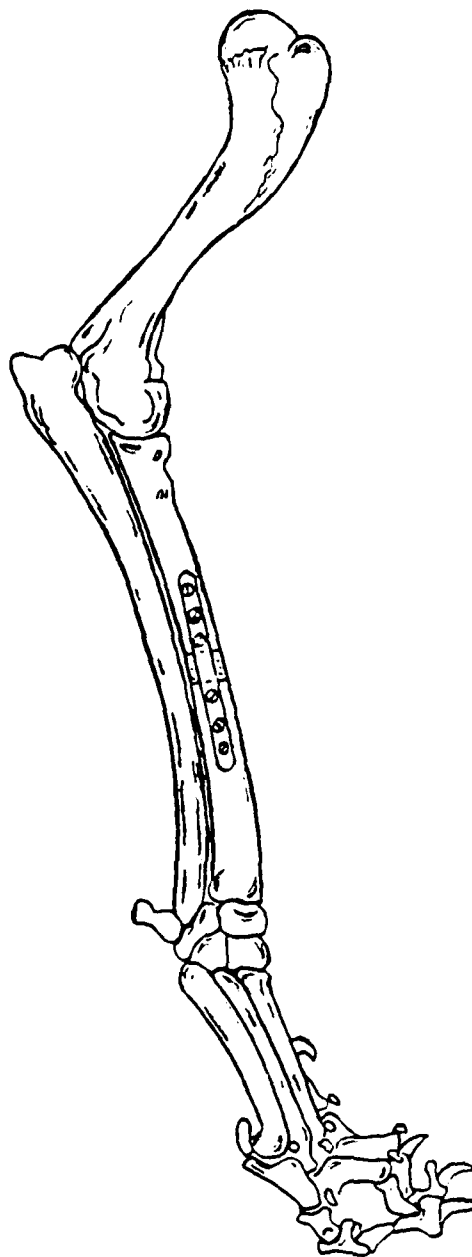


Figure 2. Schematic drawing of the segmental bone replacement and bone stabilization plate for the dog studies.

### Animal Follow-up

The surgical procedures and post operative recovery period was relatively uneventful. The anesthesia was sufficient to provide adequate surgical time and the animals moved around within their cages shortly after completion of the surgery. The animals were followed on a regular basis by the Biomaterials Laboratory and the Department of Comparative Medicine personnel. All animal procedures were approved by and checked through the Department of Comparative Medicine with the staff veterinarians. Weekly radiographs were made on all animals for times up to 6 weeks post surgery. Some series were then discontinued for 3-4 week intervals. Anterior-posterior (AP) and oblique radiographs provided the best method for routine animal evaluation. Where necessary, corrective procedures and antibiotics were used in the follow-up treatments.

### Necropsy and Histology

The animals were euthanized by drug overdose after gross observation. The tissues of interest were removed by sharp dissection and histological specimens taken. Examples of tibias and associated tissues were photographed using 35 mm color slide film. The contralateral tissues were removed in most cases to provide control samples.

Specimens were fixed in 10% neutral buffered formalin with the bone samples submitted to decalcified preparation with Hematoxylin and Eosin staining or to nondecalcified thin sectioning for general and tetracycline fluorescence evaluations. The soft tissues were submitted for routine histological evaluation.

Three of the long-term tricalcium phosphate implant rabbits were submitted to major organ evaluations conducted by our staff veterinarian - pathologist. The organs were removed, macroscopically examined, fixed and gross sectioned at the time of necropsy. The specimens were then submitted to microscopic evaluation. The organs evaluated included the lungs, kidneys, spleen and liver.

## RESULTS AND DISCUSSION

### Materials

The various TCP samples were prepared, sterilized and handled at the surgery table without difficulties. The laboratory characterizations showed porous forms with a small and large (interconnecting) porosity. The samples were relatively consistent, one to another, and from the first to second group of samples. All TCP was manufactured from the same powder and by the same process. The limited X-ray diffraction analyses also showed relatively consistent sample structures. The larger interconnecting porosity dimensions exceeded 100  $\mu\text{m}$  and provided openings for bone ingrowth.

### Surgery and Animal Follow-Up

The initial investigation (reports 1 and 2) considered segmental replacements of rabbit tibia sites (8 X 8 mm) comparing control, rod form implant and rod form implant plus electrical stimulation at 3, 6, 12 and 64 weeks. This included 60 rabbits with 15 in each group. An additional series of tibial lesions (12 X 8 mm) were prepared to develop nonunions or augmentation sites in 39 rabbits.

The nonunion and augmentation series of rabbits were implanted with rod and block forms of TCP in an attempt to correct the various bony lesions (reports 2 and 3). Three rabbits that were implanted with -40+100 mesh granular form TCP were analyzed by metabolic and organ studies.

The -40+100 mesh granular form TCP was mixed in relative amounts of 0, 50 and 100 weight percent with autogeneous bone for 8 mm and nonunion lesions in 58 rabbits (report 4). This study was further expanded to include mixtures of 1, 2 or 3 mm granular form TCP with equal quantities of autogeneous bone in another 30 rabbits (report 5).

Mid-shaft replacements of dog radii were conducted using 1 X 1 cm size rod form TCP implants in eight dogs (reports 2-5). This series was initiated to evaluate the long-term tissue reactions and biodegradation characteristics of the rod form TCP samples.

In general, no major problems with the animal surgery or follow-up procedures were encountered. The chronic nonunion rabbits were difficult to maintain with respect to pin track infections.

The rabbits in general, caused a limitation because of their relatively short life span (2-3 years) within cages. As an overall assessment of the laboratory animal models and the surgical methods, they served the objectives of the program quite well.

The specific details of the various laboratory animal procedures and complete tables of the follow-up histories have been provided in the previous reports. Because of the voluminous nature of this information, the reader is referred to these reports for more detailed explanations.

### Necropsy and Tissue Evaluations

The various TCP surgical sites showed minimal tissue reaction and good biocompatibility. At necropsy, the tissues directly adjacent to the residual TCP forms showed a passive nonreactive condition. Histological and nondecalcified sections confirmed these general observations.

In many cases, e.g. nonunions, the TCP did not result in correction of the bony lesions. It was also noted that the biodegradation rates were not the same for all specimens and the compound was not osteogenic. Some concerns have developed about residues of TCP within bone lesion sites when large quantities of the material was utilized.

Granular form TCP, when placed with autogeneous bone, shows considerable promise and may be quite valuable for the correction of selected bony lesions. The need to minimize the quantity of autogeneous bone for certain clinical cases should justify continued limited clinical trials of the granular form TCP for maxillofacial and orthopaedic applications. These need to be carefully controlled investigations.

### CONCLUSIONS

Conclusions from the investigations on porous tricalcium phosphate ceramic are as follows:

1. Biomaterial analyses showed that comparisons of structure by X-ray diffraction produced differences in relative peak intensities at selected 2 angles but relatively consistent patterns sample to sample; an interconnected porosity with an average cross section exceeding 100 micrometers; the material could be fabricated to produce implant designs; and no difficulties were encountered in sterilizing or handling the material.
2. The New Zealand White rabbit animal model provides an adequate model for initial studies on porous tricalcium phosphate ceramic for evaluation of tissue ingrowth, the role of direct current electrical stimulation, biodegradation, tissue reaction, and nonunion replacement. The ability to remove the stabilization devices at 6 weeks post surgery for most of the rabbits is the earliest time we have experienced. Most "inert" porous implants require 12-16 weeks. Immediate post operative care was uneventful; however, some transcutaneous pin tract infections were encountered after 3-6 weeks. These problems were severe for some of the long-term nonunion animals. After removal of transcutaneous devices, the remainder of the animal care was routine.
3. This rod form porous tricalcium phosphate ceramic in this animal model can serve as a scaffold with bone proliferation through the large interconnecting pores. Transverse sections showed relatively complete ingrowth of bone at 12 weeks.
4. Radiographs and gross observation at necropsy showed considerable variability in the rate of the rod form implant biodegradation. Some animals retained most of the implant after 64 weeks of implantation while others showed almost complete biodegradation. The implants showed hard and/or soft conditions by sharp probe examination. In general, the radiographic appearance of the rabbit tibias showed a steady progression toward normal anatomy after 6-12 weeks.

5. The direct current electrical stimulation resulted in more periosteal callus, and did not appear to greatly influence the tissue ingrowth and biodegradation rates for the porous tricalcium phosphate ceramic implants.
6. Biomechanical strength comparisons from four point bending and determinations of the Work to Fracture for implant and control conditions, at 3, 6, 12 and 64 weeks, showed similar ranges for the strength magnitudes at each time period. The average magnitudes of the Work to Fracture data increased with increasing time post surgery but showed a wide range within each group.
7. Rod forms of porous tricalcium phosphate ceramic implanted at nonunion sites along rabbit tibias showed a low probability for correction in that two of twenty obtained a bony union.
8. A combination of rod form porous tricalcium phosphate and autogeneous bone showed clinical union for ten out of twelve procedures for animals that could not be corrected by the tricalcium phosphate implant alone.
9. Biomechanical testing of healed nonunion rabbit tibia samples showed fracture forces from 13 to 81 pounds.
10. One long term (23 months) rabbit tibia implant showed retained ceramic at the lesion site.
11. Mixtures of granular form ceramic and autogeneous bone placed in 3 mm length lesions in rabbit tibias showed bridging of the defect at 4-6 weeks for total bone, bridging at 6 weeks for a 50/50 mixture, and bridging at 14-16 weeks for total ceramic implants. All of the lesions healed and became fully functional without stabilization devices.
12. Mixtures of granular form ceramic and autogeneous bone placed in nonunion lesions in rabbit tibias showed bridging of the defect for six of seven with total bone, bridging for two of six with a 50/50 ratio, and bridging for three of eight with total ceramic implants.
13. The granular form porous tricalcium phosphate ceramic with average dimensions of 1, 2 or 3 mm when mixed with equal weights of iliac crest autogeneous bone showed healing of an 8 mm rabbit tibial lesion for 23 or 25 intercomparable implants. No correlation with ceramic particulate size could be determined.



14. The rod form porous tricalcium phosphate ceramic implants in the mid-radius site of dogs shows continued biodegradation of the ceramic for the healed and nonunion conditions. Five dogs are healed while the new rod form ceramic implants were placed in the remaining three dogs approximately two years after initial implantation.
15. Gross observation, nondecalcified thin sectioning, standard histological sectioning and general evaluations continue to show good biocompatibility for this porous tricalcium phosphate ceramic.

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